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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,997	CARTER ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-91 and 93-134* is/are pending in the application.

4a) Of the above claim(s) *59-91 and 95-131* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93,94 and 132-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07 February 2008 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

DETAILED ACTION

Claims 1-58 and 92 have been cancelled. Claims 59-91 and 93-134 are pending. Claims 59-91 and 95-131 are withdrawn. Claims 93, 94 and 132-134 are currently examined.

Claim Rejections - 35 USC § 112, Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 93, 94 and 132-134 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained**.

Claims 93, 94 and 132-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 93, 94 and 132-134 are directed to a method of inhibiting human immunodeficiency virus (HIV) particle generation and treating AIDS in a mammalian patient comprising administering a peptide comprising a PTAP motif, said compound inhibits binding between tumor susceptibility gene (Tsg101) protein and HIV Gag polypeptide.

The breadth of the claims encompass treatment of any form of AIDS caused by the infection of any strain or subtype of HIV by inhibiting the binding of any form of Tsg101 and the Gag protein of any strain or quasi-species of HIV. With the exception of claim 132 limiting the peptide to comprise SEQ ID NO:4, the claimed peptide can be from a PTAP peptide to any protein containing the four amino acids, PTAP. Further, claims 93, 94 and 132 do not claim whether the anti-HIV peptide acts on a target that is conserved among all hosts.

The disclosure does not provide any working embodiments that meet the claimed limitations. While there is one cell culture example (page 37-41) identifying the binding regions of Gag p6 late domain and Tsg101 and mutating the binding region in either Tsg101 or Gag protein to observe the effect on particle release by HIV vector-transfected COS cells, there is no *in vitro* or *in vivo* working example that shows the effectiveness of PTAP-containing peptides in treating AIDS in mammalians.

Furthermore, the Gag p6 late domain does not represent the entire genus of the PTAP-containing peptides. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable.

The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to one cell culture assay identifying the binding regions in HIV Gag p6 late domain and Tsgl01 (Example 1) and the amount of released mature HIV particles as a result of mutated binding regions in Tsg101 and HIV Gag p6 late domain (Example 2). The disclosed example is not even a test of a peptide inhibitor for the interaction between Tsg101 and Gag. There is no evidence that shows any correlation with *in vivo* efficacy to confirm the Applicant's theory deduced from the cell culture results. There is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects. There is not even a test to determine the efficacy and resistance of the claimed genus of Tsgl01 inhibitors. An *in vitro* testing is, at most, a useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex Parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment without any knowledge of the pharmacokinetic profile, therapeutic and/or prophylactic effect in a patient. Therefore, the disclosure does not correlate with treating AIDS, especially in a human.

There is a high level of uncertainty and unpredictability in the art. The development of suitable HIV-1 or AIDS therapeutics has been an arduous and empirical process, often ending in failure (Hendrix, 2000, first and last ¶; Gait, 1995). This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro and in vivo* activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The art of HIV treatment is highly unpredictable because the effect of antiretroviral treatment appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

In the instant case, a Tsg101-Gag binding inhibitor as an AIDS drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, bioavailability, plasma concentration, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Response to Arguments

Applicant's arguments filed on 07 February 2008 have been fully considered but they are not persuasive.

Applicant argues that demonstration of *in vivo* results is not the standard of the law, *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). However, the instant case has a different fact pattern than *In re Brana*. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). See MPEP § 2164. In the instant case, the disclosure simply identifies the regions in Tsg101 and HIV Gag protein that are responsible for the binding. The disclosure does not even provide an *in vitro* binding inhibition test by the claimed PTAP-containing peptide. The prior art clearly shows a lack of correlation

between *in vitro* test results and *in vivo* efficacy, as well as a high level of unpredictability as set forth above. It is well know in the art that the development of AIDS treatment requires many *in vivo* tests to address and overcome the problems of plasma sequestration, drug targeting, viral escape through mutational replication, etc (See the rejection iterated above). Therefore, examiner has met the initial burden to give reasons for the lack of enablement and set forth ample reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example, based on the analysis of the factors as discussed *In re Wands* and the evidence as whole.

Applicant also relies on the disclosure of U.S. patent application no. 11/940,714, filed on 15 November 2007, especially page 65-72, to show that inhibition or blocking of binding between HIV and Tsg101 is effective in inhibiting HIV as a means of treatment. Contrary to Applicant's assertion, application no. 11/940,714 discloses nonanalogous art, anti-Tsg101 antibodies used for inhibiting or reducing viral infections. Anti-Tsg101 antibodies are entirely different chemical entities than the claimed peptides comprising PTAP. They not only differ in structure but also in functional characteristics with respects of binding affinities, specificities, and effective concentrations.

In response to Applicant's assertion that "the prior art issues of viral drug resistance, oral bioavailability short half-life, etc., are features of 'an agent target against the virus' not at interfering with interaction between a host protein, Tsg101, and the virus," Applicant is reminded that the claimed invention is "treating AIDS in a mammalian patient," which requires an enabling disclosure addressing the art-recognized problems of short half-life, viral escape, poor oral bioavailability, serum

protein sequestration, low plasma concentration in AIDS treatment. None of these problems was adequately addressed in the cell culture example in the instant application. Applicant is not arguing according to the claim language. Rather, Applicant is omitting limitations in the instant claims, "treating AIDS in a mammalian patient" and "reducing the amount of HIV particles generated in said mammalian patient by at least two-fold," that are not supported by the specification.

Applicant further argues that claim 132 recites a very specific agent comprising a single sequence. Nevertheless, the claimed peptide comprising SEQ ID NO:4 has not been shown in any working example to inhibit the interaction between Tsg101 and Gag of any strain of HIV in a mammalian patient, mush less a method of administering a peptide comprising SEQ ID NO:4 in an AIDS treatment.

Applicants did not provide any objective evidence that correlates the cell culture binding assay with an *in vitro* or *in vivo* inhibition and AIDS treatment. Nor have Applicants addressed the problems of AIDS treatment in order to enable the claimed method. Therefore, the instant application lacks an enabling disclosure.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Wang whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648